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Original Investigation

# The Effect of Spironolactone on Acute Kidney Injury After Cardiac Surgery: A Randomized, Placebo-Controlled Trial

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**Background:** Cardiac surgery−related acute kidney injury (AKI) is a common postoperative complication that greatly increases morbidity and mortality. There are currently no effective interventions to prevent AKI associated with cardiac surgery. Experimental data have shown that administration of the mineralocorticoid receptor blocker spironolactone prevents renal injury induced by ischemia-reperfusion in rats. The objective of this study was to test whether short-term perioperative administration of oral spironolactone could reduce the incidence of AKI in cardiac surgical patients.

**Study Design:** Randomized, double-blinded, placebo-controlled trial.

**Setting & Participants:** Data were collected from April 2014 through July 2015 at the National Heart Institute in Mexico. 233 patients were included; 115 and 118 received spironolactone or placebo, respectively.

**Intervention:** Spironolactone or placebo once at a dose of 100 mg 12 to 24 hours before surgery and subsequently 3 further doses of 25 mg in postoperative days 0, 1, and 2 were administered.

**Outcomes:** Patients were followed up for 7 days or until discharge from the intensive care unit (ICU). The primary end point was AKI incidence defined by KDIGO criteria. Secondary end points included requirement of renal replacement therapy, ICU length of stay, and ICU mortality. Data were analyzed according to the intention-to-treat principle.

**Results:** Mean age was 53.2 ± 15 years, mean serum creatinine level was 0.9 ± 0.2 mg/dL, median Thakar score for estimation of AKI risk was 2 (IQR, 1-3), and 25% had diabetes. The incidence of AKI was higher for the spironolactone group (43% vs 29%; $P = 0.02$). No significant differences were found for secondary end points.

**Limitations:** Single center, AKI was mostly driven by AKI stage 1, planned sample size was not achieved, and there was no renin-angiotensin-aldosterone system washout period.

**Conclusions:** Our trial demonstrated that spironolactone was not protective for AKI associated with cardiac surgery and there may be a trend toward risk.

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***INDEX WORDS:*** Acute kidney injury (AKI); spironolactone; cardiopulmonary bypass; cardiac surgery; mineralocorticoid receptor blocker; renal ischemia; randomized controlled trial (RCT).

Cardiac surgery with the use of cardiopulmonary bypass (CPB) is frequently practiced in hospitals worldwide for the treatment of various cardiac conditions[1] and carries a significant complications risk. Among these, postoperative acute kidney injury (AKI) is common, with a prevalence that ranges from 5% to 60% depending on the AKI definition.[1-8] It is associated with higher mortality and longer length of stay in the intensive care unit (ICU).[1-3] In addition, it has been described that AKI episodes, even if moderate, increase long-term mortality and constitute a risk factor for the development of chronic kidney disease (CKD).[9,10] For these reasons, several trials with different interventions have been attempted in patients undergoing cardiac surgery with the goal of reducing the incidence of AKI. However, these studies have been inconclusive, and there are no validated therapeutics for AKI.[11-19]

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AKI is characterized by kidney hypoperfusion and ischemia, which in turn promote activation of the renin-angiotensin-aldosterone system. It is known that the mineralocorticoid hormone aldosterone plays a major role in the development and progression of CKD through multiple mechanisms, including fibrosis, oxidative stress, endothelial dysfunction, and inflammation.[20] In addition, it is known that aldosterone by itself acts as a vasoconstrictor, which is particularly potent in the renal vasculature.[21,22] Thus, aldosterone could be an important mediator of damage during renal ischemia. In experimental studies, our group has demonstrated prevention of AKI with spironolactone before and after inducing renal ischemia. In these studies, spironolactone administration resulted in the prevention of tubular injury and reduction of oxidative stress, inflammation, and intrarenal apoptosis.[23,24]

To our knowledge, no study has evaluated the effect of spironolactone to prevent AKI in clinical studies. We sought to evaluate whether spironolactone administration before and after CPB cardiac surgery was effective to reduce the incidence of postoperative AKI.

## METHODS

### Study Design

This study was a double-blind placebo-controlled clinical trial conducted in the National Heart Institute in Mexico City. The study was approved by the Human Research and Ethics Committee of the participating center (protocol number 4182), and written informed consent was obtained from all patients. Data were collected from April 2014 through July 2015.

### Participants

Adult patients (aged ≥18 years) were eligible for the study if they were undergoing elective or emergency cardiac surgery requiring CPB, for whom the surgery was not an isolated correction of atrial septal defect. Exclusion criteria were as follows: preoperative CKD (defined as creatinine > 1.6 mg/dL), kidney transplantation or dialysis, pregnancy, hyperkalemia (potassium > 5.0 mEq/L), AKI detected up to 24 hours before the procedure, receipt of intravenous contrast agents 72 hours before surgery, and hypersensitivity, allergy, or known intolerance to spironolactone.

### Randomization

Eligible patients were assigned in a 1:1 ratio to receive either perioperative spironolactone or placebo. Randomization was performed by the Epidat 3.1 program, and allocation was implemented by a clinical research coordinator who was not directly involved with the study. Participants, care providers, and researchers were blinded to the intervention.

### Intervention

One day prior to the procedure, spironolactone or placebo was administered orally (100 mg 12-24 hours before surgery); subsequently 3 further doses of 25 mg were administered orally on postoperative days 0, 1, and 2. If mechanical ventilation continued, spironolactone was administered through a nasogastric tube. Criteria for stopping the intervention were serum potassium level > 5.5 mEq/L, serum creatinine level ≥ 2.5 mg/dL, urine output < 0.3 mL/kg/h during the care shift immediately before the drug administration, or requirement for renal replacement therapy. In our institution, patients receiving angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics usually have these medications discontinued the day before surgery. These medications were managed independently by the treating physician without any suggestion from the investigators.

### Outcomes and Assessment

All known pre- and intraoperative risk factors associated with AKI in a previous cohort from our institute were assessed.[25] Urinary electrolytes were measured the day prior to the surgery before the 100 mg of spironolactone was administered, and on the day of the surgery immediately prior to the surgery, urine was collected in the operating room through a Foley catheter. AKI postoperative risk was estimated with the scale described by Thakar et al,[26] which is a standardized scale to assess dialysis risk after cardiac surgery.

Serum urea nitrogen, serum creatinine, and potassium were measured daily until postoperative day 7 or discharge from the ICU, whichever occurred first. Urine output was measured every shift. The primary outcome was the development of AKI defined by KDIGO (Kidney Disease: Improving Global Outcomes) criteria (stage 1, 2, or 3 depending on urine output and/or creatinine criteria).[27] Secondary outcomes included requirement of renal replacement therapy, length of stay in the postoperative ICU, and mortality. Patients were followed up until they were discharged from the ICU.

### Statistical Analysis

Quantitative variables with parametric distribution were expressed as mean ± standard deviation. Sample size was estimated based on a 15% AKI difference between groups, requiring 141 patients per group for a 95% confidence level and 80% power. Variables with non nonparametric distribution were expressed as median (interquartile range [IQR]). Normality tests were performed by Shapiro-Wilk and Kolmogorov-Smirnov. Qualitative variables were presented as number and percentage and were compared between intervention groups using $t$ or Mann-Whitney $U$ tests. Categorical variables, including primary and secondary outcomes, were compared using Pearson $\chi^2$ test. Variables with a significant difference between groups at baseline were introduced in a logistic regression model for AKI using the "forward" method, accomplishing an event to parameter ratio > 10. In case of continuous independent variables not fitting linearity in the multivariable analysis, they were split into categories decided through receiver operating characteristic curve analysis. $P < 0.05$ was considered significant.

Statistical analyses were performed using the statistical package SPSS Statistics, version 16.0 (SPSS).

## RESULTS

### Study Participants

Two hundred forty-eight patients were recruited. Fourteen patients were not included in the analysis due to a surgery scheduling delay after the first dose of spironolactone or placebo was administered, and another patient was transferred to a different facility a few hours after the surgery. Two hundred thirty-three patients were included: 115 in the spironolactone group and 118 in the placebo group (Fig 1). Mean age was 53.2 ± 15.1 (standard deviation) years, 58% were men, and 25% had diabetes. Mean baseline creatinine